12/17/98

MEMORANDUM

Subject: **Cadusafos** (PC Code 128864). HED Risk Assessment for the Risk Management Proposal

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This memorandum supersedes the 7/17/98 HED risk assessment for cadusafos and provides revised risk estimates for acute and chronic dietary exposure. Potential dietary exposure is the only Agency consideration at this time since there are no current US registrations for domestic use. Cumulative risk assessment, considering other pesticides with a common mechanism of action (cholinesterase inhibition), is not addressed in this memorandum. The following attachments provide detailed information and conclusions on which the risk assessment is based:

CADUSAFOS - Report of the FQPA Safety Factor Committee (B. Tarplee, 12/7/98).

Cadusafos Anticipated Residues (J. Punzi, 12/17/98)

O-ethyl S,S-di-sec-butyl phosphorodithioate (Document Eligibility Review including Acute Delayed Neurotoxicity in the Hen. R. Landolt memo, 4/25/85)

Also attached are Dietary Exposure Evaluation Model (DEEM) summary tables.

Background

Cadusafos [O-ethyl S,S-bis (1-methylpropyl) phosphorodithioate] is a nematicide, manufactured by the FMC Corporation under the trade name "Rugby". Cadusafos is used for the control of parasitic nematodes and soil insects. An import tolerance for residues of cadusafos in/on bananas was established through a petition (6E03447) submitted by the FMC Corporation in 1986. Establishment of a three-year import tolerance of 0.02 ppm was originally proposed. For purposes of harmonization with the proposed Codex MRL for bananas, the Agency approved a two-year time-limited tolerance of 0.01 ppm. The time-limited tolerance was converted to a permanent tolerance after the Agency reviewed confirmatory usage data (i.e., application rate) required to ensure that cadusafos would be applied to bananas in a manner that would not exceed the residue level proposed for tolerance.

The Biological and Economic Analysis Division (BEAD) estimates (S. Smearman memo, 11/13/98) that 10 to 15 percent of the annual banana imports into the US will have been treated with cadusafos. The primary countries exporting cadusafos treated bananas are Guatemala, Costa Rica, Ecuador, and Honduras.

Hazard Identification

Cadusafos is an aliphatic organophosphate and does not require bioactivation in the liver, as do sulfur-organophosphates. Cadusafos is readily absorbed by all routes of exposure (oral, dermal, and inhalation). The toxic residue of concern is the *parent* compound.

It is well documented that Cadusafos is severely acutely toxic and, similar to all organophosphate chemicals, is a potent inhibitor of acetylcholinesterase (AchE) at nerve endings in mammalian central and peripheral nervous systems. Animal studies (acute) indicate that lethality occurs at low doses regardless of the route of administration. Death results at similar doses in acute oral, dermal, and inhalation studies in several mammalian species; oral LD_{50} = 30 mg/kg in rats; dermal LD_{50} = 24 mg/kg in rabbits; acute inhalation LC_{50} = 0.03 mg/L in rats. Death occurred within 24 hours with cholinergic overstimulation (respiratory failure) as the primary cause of death. All animals exhibited the onset of signs of cholinergic toxicity (excess salivation, lacrimation, ataxia, chromodacryorrhea, tremors, decreased activity, labored breathing, and finally death) within 2 hours of receiving the oral dose.

In addition to the acute toxicity via the oral, dermal, and inhalation routes, death occurred in rabbits receiving a low dose of cadusafos via the eye. Again, signs of cholinergic toxicity were noted prior to death; ataxia, increased locomotion, rales, hypersensitivity, grinding of teeth, and oral discharge. Reviewed data indicates no significant sex-related differences in cadusafos' toxicity. Dose-related inhibition of plasma, red blood cell (RBC) and brain cholinesterase occurs in dogs and rats by all routes following acute, subchronic and chronic exposures. Dogs are the more sensitive species to cholinesterase inhibition in subchronic and chronic oral studies.

Cadusafos is classified as a Group E (i.e. the chemical is characterized as "not likely" to be a carcinogen in humans via relevant routes of exposure) based on carcinogenicity studies in rats

and mice.

Considerations for special sensitivity in infants and children (FQPA)

To address the Food Quality Protection Act requirement for an additional safety factor to protect infants and children, the HED Hazard Identification Assessment Review Committee (HIARC) reviewed the cadusafos toxicity database for evidence of neuropathology which may indicate an increased susceptability of the developing nervous system to cadusafos. Also examined for indications of enhanced sensitivity were developmental studies in rats and rabbits, and a reproduction study in rats.

In an acute delayed neurotoxicity study, hens received an oral administration of a single dose of cadusafos at 8 mg/kg/day. Cadusafos did not cause delayed neurotoxicity and showed no evidence of neuropathology in hens. It is noted that this study did not assess for the potential of cadusafos to inhibit neurotoxic esterase (NTE) in hens (MRID 00255691).

Developmental toxicity studies in rats and rabbits show no evidence of additional sensitivity in young rats or rabbits following pre- or post-natal exposure to cadusafos and comparable NOELs were established for adults and offspring.

The results of the two-generation reproduction study in rats (MRID 41441803) were re-evaluated during the 4/22/98 HIARC meeting to address an apparent increase in susceptibility (decrease in live birth index) to offspring following exposure to cadusafos. The Committee concluded that although there is an apparent dose-related decrease in the live birth index in the F_{2B} generation, there was no such incident pattern observed in any other generation and no significant increased sensitivity to pups over adults.

No acute or subchronic neurotoxicity studies are available and thus data on cholinesterase inhibition, Functional Observational Battery (FOB), and histopathology on the central and peripheral nervous systems are not available for evaluation after single or repeated exposures to cadusafos.

FQPA Safety Factor: Initially, the HIARC (6/4/98) and the FQPA Safety Factor Committee (8/6/98) in their respective meetings, determined that the 10x safety factor should be retained for cadusafos because of neurotoxicity datagaps, as well as for the placement of the developmental neurotoxicity study in rats *in reserve*. However, following these meetings, data for the acute delayed neurotoxicity was made available which made this study acceptable and satisfactory for the Agency Guideline requirement. Taking this information into consideration, on September 22, 1998, the FQPA Safety Factor Committee recommended that the 10x factor for protection of infants and children (as required by FQPA) should be reduced to 3x for cadusafos. The requirement for a Developmental Neurotoxicity Study in Rats remains *in reserve.*

Endpoints / doses for dietary risk assessment:

Acute Reference Dose: The Agency has established a Reference Dose of 0.00007 mg/kg body weight/day to assess the risk associated with acute dietary exposure(s) to cadusafos. Lacking adequate studies to evaluate the toxicity of cadusafos after a single exposure (acute neurotoxicity in rats), a weight-of-evidence approach was applied to estimate a toxicological endpoint and dose for acute dietary risk assessment. The acute RfD is based on the results of the 14-day (range finding) oral toxicity study in dogs (MRID 40017902). This study established a NOEL of 0.02 mg/kg/day based on plasma ChE inhibition at 0.1 mg/kg/day (LOEL) in both sexes, observed on Day 3. Plasma ChE inhibition is determined to be the most sensitive indicator of cadusafos toxicity in this study and, based on the onset of signs of cholinergic toxicity noted in other acute toxicity studies (within 2 hours post dose), it is reasonable to assume that this critical effect also occurred on Day 1 although ChE activity was not measured at this point in the study.

An Uncertainty Factor (UF) of 300 has been determined for cadusafos based on: 10x for interspecies extrapolation; 10x for intraspecies variation; and 3x (FQPA) for the lack of acute/subchronic neturoxicity data.

Chronic: The Agency has established a *chronic* Reference Dose of 0.000003 mg/kg body weight/day to assess the risk associated with chronic dietary exposure to cadusafos. The chronic RfD is based on the NOEL of 0.001 mg/kg/day (for plasma cholinesterase inhibition observed at 0.005 mg/kg/day) established in a one-year feeding study in dogs (MRIDs 40017901/40017902).

An Uncertainty Factor (UF) of 300 has been determined for cadusafos based on: 10x for interspecies extrapolation; 10x for intraspecies variation; and 3x (FQPA) for the lack of acute/subchronic neturoxicity data.

Product Chemistry Data Requirements:

All pertinent data requirements are satisfied for the FMC 92% T/TGAI provided that the registrant submits data required for Guidelines 830.1700 (Preliminary Analysis) and 830.7050 (UV/Visible Absorption).

Dietary Exposure / Residue Estimates for Risk Assessment:

HED concludes (R. Landolt memo, 2/15/91) that terminal residues in banana pulp (hydroxy-2-butyl methyl sulfone and 2-butyl methyl sulfone) are not of toxicological concern. The residue of concern is parent *only*.

The data requirements for “magnitude of the residue” in bananas have been fulfilled. The Agency has evaluated the results of residue field trails conducted in seven sites (in the Ivory Coast, Costa Rica, the Philippines, Guatemala, and Honduras). Residues of cadusafos were not detected (<0.005 ppm) in treated banana pulp samples harvested 1 to 211 days following application of the granular formulation at 6 g ai./mat/year (1x the maximum established seasonal rate) or at exaggerated rates (1.3x and 6.7x). Three samples of treated banana peel exhibited

finite residues (0.005 ppm); each of these values resulted from an exaggerated application rate and a short PHI.

Since 1993, the Food and Drug Administration (FDA) has analyzed hundreds of samples, from approximately a dozen countries, for residues of cadusafos. The FDA reports no detections of cadusafos using a Multi Residue Method (MRM).

Based on the available data, HED concludes that the appropriate residue values for acute and chronic dietary risk assessment should be based on the results of a ^{14}C metabolism study and the LOD of an Agency validated enforcement method for cadusafos, respectively. This assessment uses the LOD of 0.001 ppm for acute dietary risk assessment and ½ LOD (0.0005 ppm) for chronic risk assessment. The value of 0.001 ppm represents a probable upper-end estimate of cadusafos residues in banana *pulp*. Use of the LOD derived residue levels for risk assessment is consistent with the HED Chemistry Science Advisory Council (ChemSAC) guidance of 5/19/98. The Agency does not have sufficient data to conclude, at this time, that "zero" parent residue is present in cadusafos-treated banana pulp.

Dietary Risk Estimates:

The *Dietary Exposure Evaluation Model (DEEM)*, based on 1989-92 USDA food consumption data, was used to estimate acute and chronic risk for cadusafos. DEEM replaces the DRES program which is based on 1977-78 food consumption data. The DEEM model calculates exposures based on single-day (rather than single-serving) consumption data.

Acute risk: The following acute risk estimates are considered upper-end estimates since the residue level assumed is a point estimate (0.001 ppm) rather than a range, and percent crop treated information (15%) is not used.

Based on the above, DEEM estimates that the "Average U.S. Population" and the population subgroups of "All Infants (<1 year)" and Children (1-6 years) are exposed to cadusafos (per day) at a level less than the cadusafos acute RfD (less than 20% at the 95th Percentile for both groups). The population group "All Infants" is noted since this group is typically estimated to be the most highly exposed group and satisfies the FQPA requirement for the special consideration of pesticide risk to children.

Chronic risk: The following chronic risk estimates are based on the residue level of ½ LOD (0.0005 ppm), the upper-end of the crop treated estimate (10-15%), and *averaged* food consumption estimates. The resultant risk estimate is not considered upper-end since the estimate is refined by the percent crop treated data.

Based on the above, DEEM estimates that the "Average U.S. Population" and all population subgroups including "All Infants (<1 year)" are chronically exposed to cadusafos at a level less than the cadusafos chronic RfD (less than 5% for all population groups).

Based on the above, the Agency concludes that potential acute or chronic dietary exposure to cadusafos is less than the level of concern for all US citizens including infants and children .

Attachments:
Attachment 1 - DEEM exposure/risk summaries
Attachment 2 - *CADUSAFOS - Report of the FQPA Safety Factor Committee* (B. Tarplee, 12/7/98).
Attachment 3 - *Cadusafos Anticipated Residues* (J. Punzi, 12/17/98)
Attachment 4- *O-ethyl S,S-di-sec-butyl phosphorodithioate* (Document Eligibility Review including Acute Delayed Neurotoxicity in the Hen. R. Landolt, 4/25/85)

DEEM SUMMARY TABLES

Residues for Acute Dietary Risk Estimates

CHEMICAL NAME: Cadusafos (1989-92 data)
RfD(ACUTE): .000070 mg/kg/DAY NOEL(ACUTE): .020000 mg/kg/day
Comment: Uncertainty Factor for Acute/Chronic RfD is 300 for Data Gaps

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	RDF #	Adj.Factors #1	Adj.Factors #2
073	A	BANANAS-DRIED	000.001000	1	03.900	01.000
378	A	BANANAS-JUICE	000.001000	1	01.000	01.000
072	A	BANANAS	000.001000	1	01.000	01.000

Acute Dietary Risk Estimates

Summary calculations:

	95th Percentile Exposure	95th Percentile % aRfD	99th Percentile Exposure	99th Percentile % aRfD	99.9 Percentile Exposure	99.9 Percentile % aRfD
U.S. pop - all seasons:						
	0.000002	2.62	0.000005	7.55	0.000015	20.93
All infants (<1 year):						
	0.000014	19.66	0.000017	24.75	0.000022	31.48
Children (1-6 years):						
	0.000006	8.90	0.000011	15.61	0.000027	39.10

Residues / Percent Crop Treated for Chronic Risk Estimates

CHEMICAL NAME: Cadusafos
RfD(CHRONIC): .000003 mg/kg/DAY NOEL(CHRONIC): .001000 mg/kg/day
Comment: Uncertainty Factor for Acute/Chronic RfD is 300 for Data Gaps

Food Code	Crop Grp	Food Name	RESIDUE (ppm)	Adj.Factors	
073	A	BANANAS-DRIED	000.000500 (½ LOD)	3.900	0.150 (%crop treated)
378	A	BANANAS-JUICE	000.000500 (½ LOD)	1.000	0.150 (%crop treated)
072	A	BANANAS	000.000500 (½ LOD)	1.000	0.150 (%crop treated)

Chronic Dietary Risk Estimates

DEEM89N CHRONIC analysis for CADUSAFOS (1989-92 data)
Reference dose (RfD, CHRONIC) = 0.000003 mg/kg body-wt/day
COMMENT 1: Uncertainty Factor for Acute/Chronic RfD is 300 for Data Gaps

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Percent of Rfd
U.S. Pop - 48 states - all seasons	0.000000	0.7%
U.S. Population - spring season	0.000000	0.7%
U.S. Population - summer season	0.000000	0.6%
U.S. Population - autumn season	0.000000	0.7%
U.S. Population - winter season	0.000000	0.9%
Northeast region	0.000000	0.7%
Midwest region	0.000000	0.7%
Southern region	0.000000	0.8%
Western region	0.000000	0.8%
Pacific Region	0.000000	0.8%
Hispanics	0.000000	0.7%
Non-hispanic whites	0.000000	0.7%
Non-hispanic blacks	0.000000	0.6%
Non-hispanic other than black or white	0.000000	1.1%
All infants (<1 year)	0.000000	3.8%
Nursing infants (<1 year)	0.000000	1.7%
Non-nursing infants (<1 year)	0.000000	> 4.6%
Children (1-6 years)	0.000000	2.1%
Children (7-12 years)	0.000000	0.8%
Females (13-19 yrs/not preg. or nursing)	0.000000	0.4%
Females (20+ years/not preg. or nursing)	0.000000	0.6%
Females (13-50 years)	0.000000	0.4%
Females (13+/pregnant/not nursing)	0.000000	0.6%
Females (13+/nursing)	0.000000	0.8%
Males (13-19 years)	0.000000	0.5%

Males (20+ years)	0.000000	0.4%
Seniors (55+)	0.000000	0.8%